201-14329

PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS

HEADQUARTERS
501 FRONT STREET
NORFOLK, VA 23510
TEL 757-622-PETA
FAX 757-622-0457

March 4, 2003

Christine Todd Whitman, Administrator
US Environmental Protection Agency
Ariel Rios Bldg., Rm. 3000 (1101A)
1200 Pennsylvania Ave., NW
Washington, DC 20460

Re: Comments on the HPV test plan for hexamethoxymethylmelamine

Dear Administrator Whitman:

The following are comments on the test plan prepared by the HMMM Coalition, consisting of Borden Chemical, Inc., Cytec Industries, Inc., and Solutia, Inc. These comments are submitted on behalf of People for the Ethical Treatment of Animals (PETA), the Physicians Committee for Responsible Medicine, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These animal, health, and environmental protection organizations have a combined membership of more than ten million Americans.

The test plan in question is primarily for the monomer hexamethoxymethylmelamine (HMMM), also known as 2,4,6-tris[bis(methoxymethyl)amino]-1,3,5-triazine (CAS no. 3089-11-0). The HMMM Coalition has decided to categorize some or all HMMM polymers (including the dimer and trimer) together with the monomer, on the basis of their similar structures. It has included in the test plan the "low-molecular-weight polymeric HMMM" of which one of Solutia's commercial formulations is composed, on the grounds that it "is very similar to the monomeric form of HMMM" (test plan, p. 3). In addition, as commercial formulations of HMMM are complex mixtures (test plan, pp. 3, 5, 7), the HMMM Coalition has decided not to carry out the tests on pure HMMM, but on a commercial formulation prepared by Cytec, containing approximately 50% HMMM, and approximately 50% a related melamine derivative, CAS no. 68002-20-0 (test plan, pp. 3, 7). We welcome these decisions, and we would like to support them by emphasizing that (i) structurally and chemically similar compounds should be included in a single category, and (ii) when compounds are not usually handled in the pure form (e.g. in commercial use), their toxicity is academic, and the crucial issue is the toxicity of the commercial formulation.

The HMMM Coalition has recognized that, with respect to most of the endpoints covered by the HPV Program, relevant data of acceptable quality are already available for HMMM and its commercial formulations. Numerous mammalian tests have already been carried out, including four oral acute toxicity tests in rats, two dermal irritation tests in rabbits, and one each of the following: an acute dermal toxicity study in rabbits, an acute inhalation study in rats, a rabbit eye irritation test, a 28-day dermal repeat-dose study in rats, and a rat bone marrow cytogenetics test (test plan, pp. 6-9, summaries, pp. 28-51). Experimenters were unable to detect any effects at extremely high dose levels, including some at the limit dose of 1,000 mg/kg/day. However, two additional areas remain for which no SIDS data have been identified: reproductive and developmental toxicity. The test plan therefore states that a combined repeat-dose/reproductive/

developmental toxicity test will be carried out, in accordance with OECD Guideline 422, in order to generate the required data (p. 4). This test will kill at least 675 mammals.

Our first concern with the testing proposal is that serious toxicity due to the HMMM category appears unlikely. The four oral acute toxicity tests showed HMMM to have "essentially no toxicity" (test plan, p. 6), and the dermal tests yielded no evidence of local irritation or systemic toxicity, with the no-observed-adverse-effect level in the 28-day test being as high as 1,000 mg per kilogram of body weight per day, which is usually considered to be the limit dose (summaries, pp. 40-41). Among all the tests, the most severe toxicity observed was slight eye irritation in rabbits (summaries, p. 35). Therefore, as far as any weight may be placed on animal tests, it is reasonable to expect HMMM to have very low toxicity. Further, the fact that extensive histopathological examinations are included in 28-day repeat dose studies (the study submitted in this test plan was GLP), and there is no evidence of systemic or target organ toxicity, lends further support to the claim that subjecting many hundreds of animals to suffering in additional toxicity tests in this screening level program will not yield meaningful information.

If, improbably, HMMM commercial formulations do have significant toxicity, the ingredient most likely to be responsible is formaldehyde. All formulations of HMMM and other melamine-formaldehyde resins contain at least small amounts of formaldehyde, which is universally accepted as being highly toxic (Fielder 1981, Clary 1982, Gibson 1983, Warlew 1983). However, we have no official information about the formaldehyde concentration of the formulation to be tested, or the differences between commercial formulations in this respect. The test plan provides no analytical chemical data for the various commercial formulations. This absence makes it difficult to discuss the possibility of formaldehyde toxicity, and the possible need for further testing.

Although it is unlikely that formulations containing only very small amounts of formaldehyde have serious health effects on the occupationally exposed, one epidemiology study of workers exposed to a resin similar to HMMM suggests that this possibility cannot be excluded. This study showed that the workers had increased urinary excretion of formic acid (the principal formaldehyde metabolite), and increased rates of respiratory, gastrointestinal, musculoskeletal and cardiovascular problems, despite having an estimated chronic formaldehyde exposure of only 0.025 ppm (Srivastava 1992). This exposure is only 3.3% of the current 8-hour time-weighted-average US occupational exposure limit for formaldehyde in air (OSHA). This finding epitomizes the fact that it is difficult to discuss HMMM toxicity meaningfully until detailed exposure and epidemiology studies have been carried out on occupationally exposed populations. This is true even if HMMM formulations present no risk of formaldehyde toxicity. During the period 1981-1983, it is estimated that more than 40,000 people in the USA, including more than 7,000 women, were occupationally exposed to HMMM (NIOSH), suggesting that there would be little practical difficulty involved in carrying out exposure and epidemiology studies, covering possible reproductive and developmental toxicity.

We must stress that, particularly with respect to reproductive and developmental toxicity, Srivastava's epidemiological findings do *not* provide support for conducting further animal studies on HMMM formulations and other materials containing low concentrations of formaldehyde. The toxicity of formaldehyde has been demonstrated in innumerable animal

studies, but animal studies have not generally supported the possibility of reproductive or developmental toxicity (Clary 1982). Certain human epidemiology studies, on the other hand, have suggested that women with occupational exposure to formaldehyde, such as carpenters and hairdressers, suffer problems such as decreased fertility (Taskinen 1999), menstrual disorders (Barlow 1981), spontaneous abortion (John 1994), and low-birth-weight babies (Maroziene 2002). Once again, this emphasizes the need for human exposure and epidemiology studies, not new animal studies.

Finally, the probable absence of data for HMMM and its commercial formulations with respect to the SIDS developmental toxicity endpoints does not, in itself, present a case for carrying out additional animal experiments. Developmental and reproductive toxicity tests in animals have not been validated for humans. We therefore strongly recommend that *in vitro* studies be used instead of animal studies. An *in vitro* embryotoxicity test method, the rodent embryonic stem cell test, has in fact recently been validated by the European Centre for the Validation of Alternative Methods, and the Centre's Scientific Advisory Committee has concluded that this test is ready to be considered for regulatory purposes (Genschow 2002). We therefore urge the HMMM Coalition to consider the use of this *in vitro* test. If a positive result is found in the embryonic stem cell test, HMMM should be treated as a development toxicant/teratogen, and no further testing should then be carried out within the screening-level program. Although we have written to the EPA repeatedly concerning the inclusion of the embryonic stem cell test in the HPV Program, with correspondence dating back more than six months, we have received no reply. We urge the HMMM Coalition to correspond directly with the EPA on the incorporation of this validated non-animal test.

To summarize: (i) existing data show that HMMM has a very low toxicity, (ii) any toxicity is likely due to the formaldehyde content, (iii) chemical analytical data for the commercial formulations (e.g., formaldehyde content) are vital for meaningful analysis; (iv) epidemiology studies on humans exposed to HMMM formulations would yield more meaningful information to assess human hazard; and (v) *in vitro* tests should be used.

Given the information presented above, and the fact that understanding and reducing exposure to humans is more important than obtaining new toxicity data on the effects of HMMM in rodents, it is worth reiterating the following three provisions of the October 1999 agreement to reduce the number of animals killed in the HPV Program:

(1) In analyzing the adequacy of existing data, participants shall conduct a thoughtful, qualitative analysis rather than use a rote checklist approach. Participants may conclude that there is sufficient data, given the totality of what is known about a chemical, including human experience, that *certain endpoints need not be tested*

(3) Participants shall maximize the use of scientifically appropriate categories of related chemicals and structure activity relationships.

(8) ... As with all chemicals, before generating new information, participants should further consider whether any additional information obtained would be *useful or relevant.*

Thank you for your attention to these comments and we look forward to your response. I can be reached at 757-622-7382, extension 1304, or via e-mail at JessicaS@peta.org.

Sincerely,

Jessica Sandler, MHS
Federal Agency Liaison
PETA

Richard Thornhill, PhD
Research Associate
PETA Research and Education Foundation

References

Barlow, S., "Work and sex", *Med. World* 119: 16-17, 1981.

Clary, J.J., "Review of general health effects of formaldehyde," 75th Annual Meeting of Air Pollution Control Association, paper no. 82-30.5, 1982.

Fielder, R.J., *et al.*, *Formaldehyde* (Toxicity Review 2), Health & Safety Executive, Her Majesty's Stationery Office, London, 1981.

Genschow, E., *et al.*, "The ECVAM international validation study on *in vitro* embryotoxicity tests: Results of the definitive phase and evaluation of prediction models," *Altern. Lab. Anim.* 30: 151-76, 2002.

Gibson, J.E., *Formaldehyde Toxicity*, Hemisphere Publishing, New York, 1983.

John, E.M., *et al.* "Spontaneous abortions among cosmetologists," *Epidemiol.* 5: 147-155, 1994.

Maroziene, L., *et al.*, "Maternal exposure to low-level air pollution and pregnancy outcomes: a population-based study," *Env. Health* 1: 6, 2002.

NIOSH (National Institute for Occupational Safety and Health), "National Occupational Exposure Survey (1981-1983): Hexamethoxymethylmelamine," http://www.cdc.gov/noes/noes1/m0774sic.html.

OSHA (Occupational Safety and Health Administration), US Dept. of Labor, 29 CFR Standard 1910.1048, http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10075

Srivastava, A.K., *et al.*, "Clinical evaluation of workers handling melamine formaldehyde resin," *J. Toxicol. Clin. Toxicol.* 30: 677-681, 1992.

Taskinen, H.K., *et al.*, "Reduced fertility among female wood workers exposed to formaldehyde," *Am. J. Ind. Med.* 36: 206-212, 1999.

Warlew, G.A., "The health hazards of formaldehyde," *J. Appl. Toxicol.* 3: 121-126, 1983.